



USAID
FROM THE AMERICAN PEOPLE

REPORT TO CONGRESS

**The USAID Strategic Plan for
Microbicide Research and Development:
Current Initiatives and Next-Generation Leads**

SEPTEMBER 2009

Table of Contents

- Acronymsi**
- Executive Summary1**
- I. The Need for a Microbicide for Women in Developing Countries5**
- II. Microbicides and Health Product Research at USAID5**
- III. The Coordination of the USAID Microbicide Program
and Collaborations with Other USG Agencies and Stakeholders7**
- IV. The Milestones and Progress to Date of the USAID Program8**
- V. The Current Priorities of the USAID Microbicide Program9**
- VI. The Review, Selection, and Management of Activities Funded
by the USAID Microbicide Program10**
- VII. The Strategic Plan for Continuing Progress
with Current Initiatives12**
- VIII. The Strategic Plan for Advancing the Best Next-Generation
Microbicide Leads16**
- IX. The Strategic Plan and Accomplishments to Support Introduction,
Distribution, and Use of Microbicides18**
- X. Looking Forward Programmatically21**

Acronyms

API	Active Pharmaceutical Ingredients
ARV	Antiretroviral
CA	Cooperating Agency
CAPRISA	Centre for the AIDS Programme of Research in South Africa
CDC	Centers for Disease Control and Prevention
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
FY	Fiscal Year
IND	Investigational New Drug Application
IPM	International Partnership for Microbicides
NDA	New Drug Approval
NGO	Nongovernmental Organization
NIH	National Institutes of Health
OGAC	Office of the Global AIDS Coordinator
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
R&D	Research and Development
STI	Sexually Transmitted Infection
USAID	U.S. Agency for International Development
USG	United States Government
USG Plan	U.S. Government Strategic Plan for Microbicide Development

Executive Summary

Health research is integral to the ability of the U.S. Agency for International Development (USAID) to achieve its development objectives worldwide. Past USAID research investments have led to products that today reach millions of people, saving lives throughout the developing world. As a key implementer of the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), USAID plays a critical role in shaping the strategic and technical direction of microbicide research and development (R&D) to meet developing-country needs.

Although effective treatment programs will help, the greatest impact in mitigating and eventually reversing the HIV/AIDS pandemic will ultimately be through the development and introduction of new prevention technologies. Microbicides are entirely new products that, when available, will provide women with an effective barrier to sexually transmitted HIV and possibly other sexually transmitted infections (STIs). An effective microbicide will help fill the enormous need for a new prevention option for women and complement other existing or new prevention approaches. For more than a decade, the USAID has supported the research needed to develop safe, effective, and acceptable microbicides that are low in

cost, have appropriate characteristics for use in developing countries, and can be provided through public-sector programs.

USAID's strategy for microbicide R&D focuses on moving the most promising and appropriate candidate products available into advanced testing. Clinical trials demonstrating the safety and effectiveness of these products must be completed in order for them to be approved by appropriate regulatory agencies and introduced into prevention programs. USAID's extensive field presence and experience in collaboration and research in developing countries, including in populations with very high rates of HIV incidence (where clinical trials of microbicides must be conducted), are highly instrumental in this effort. USAID is also uniquely positioned to leverage and coordinate the intellectual, proprietary, and financial resources of a wide range of contributors, including other public-sector agencies, private foundations, and commercial partners.

To date, the USAID microbicide program has made significant progress built on rigorous preclinical evaluations, selection of the most appropriate active agents, and formulation of the best leads for clinical testing in humans. Since 2004, USAID has moved five prom-

ising candidates – Savvy™ (C3IG), Ushercell™ (cellulose sulfate), Carraguard™, Tenofovir 1% Vaginal Gel, and oral Truvada™ in women – through the early stages of clinical testing for safety in humans (Phase I and II trials) and into the advanced stages of clinical testing to evaluate the candidate’s effectiveness in reducing the risk of HIV infection as well as to assess its acceptability to users and provide additional safety data (Phase IIb and III trials). Although three of these trials have now been either completed (Carraguard) or stopped (Savvy, due to low HIV incidence at trial sites, and Ushercell due to an unexpected indication of potential harm) without detecting protective effects, these trials have demonstrated for the microbicide field the feasibility and best practices of conducting large trials with extensive community involvement in developing countries.

The Phase IIb and III trials currently underway with Tenofovir 1% Vaginal Gel (in the CAPRISA 004 trial) and Oral Truvada (a combination of Tenofovir and emtricitabine in the FemPreP trial) will continue with fiscal year (FY) 2009 support as part of the USAID strategic plan for microbicide R&D. These trials, which will be completed in 2010 and 2012, respectively, employ specific antiviral agents and unique delivery regimens that should increase both user compliance and product effectiveness. These large clinical studies are conducted in collaboration with other agencies and donors to share costs and maximize the speed and efficiency of this work.

While completion of these ongoing clinical trials is the highest USAID priority, there are additional research priorities that are also critical in addressing technical and other needs in the microbicide field. These include: novel delivery methods, combination products including multiple-mechanism and multiple-purpose agents, development of new and existing leads, optimized clinical trial design and management, clinical trial site coordination, alternative trial designs, and post-trial access issues. These research priorities are reviewed and updated at least annually and shared with USAID partners and the field to stimulate creative approaches to meet needs and solve problems in microbicide R&D.

To ensure the coordination of federally-sponsored microbicide R&D, USAID consults frequently with other U.S. Government (USG) agencies, including the National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and Food and Drug Administration (FDA). USAID partners with these other USG agencies in developing and implementing the U.S. Government Strategic Plan for Microbicide Development (the USG Plan), and contributes to the following government-wide objectives:

- Preclinical development and evaluation of potential microbicide candidates
- Formulation and delivery of potential microbicides
- Clinical testing of microbicides

- Behavioral and social science research
- Provision of training and infrastructure

For the microbicide field, this collaborative approach has been both productive and successful in coordinating protocols for preclinical testing, prioritizing promising candidates, designing clinical trials, building local research capacity, and preparing communities for clinical studies, as well as learning about each other’s progress, the state of the art, and best practices, including standards of care. This coordination fosters the strategic implementation of all research, ensures the best use of federal resources, and prevents unnecessary duplication of effort.

In the review and funding of microbicide activities, USAID strives for clarity and transparency and seeks stakeholder participation at every stage of R&D. Microbicide funds are generally provided through five-year cooperative agreements that include substantial involvement of USAID technical staff to ensure appropriate use of funds and timely progress. Activities are funded for only one year at a time and require an annual review of progress, future work plans, and budget to receive additional funding. Partners are usually selected through competitive procurements, but may be selected noncompetitively when justified by their predominant technical capability, proprietary products, or other unique intellectual property.

For FY 2008, USAID funding for microbicide R&D totaled \$44,636,000 and was distributed strategically to each of the USG objectives as follows: preclinical development and evaluation – \$9,757,000 (22%), formulation and delivery – \$7,847,000 (18%), clinical testing – \$17,731,000 (39%), behavioral and social science – \$2,933,000 (7%), research infrastructure – 6,368,000 (14%). The supported activities target the discovery, characterization, and development of new active agents; the development of new formulations and delivery systems to enhance product acceptability and use; the advancement of clinical testing of the most promising leads; behavioral studies of acceptability and product use in trials; and the capacity building needed to strengthen investigators and trial sites in developing countries.

The USAID strategic plan for developing the best next generation microbicides includes these objectives combined with efforts to reduce product cost, understand and avoid the risk of viral resistance to active agents, broaden the range of active agents with alternative and complementary mechanisms of action, and sustain capacity for characterizing promising early-stage leads.

USAID is simultaneously addressing policy and logistical issues that will be critical to the successful introduction of microbicides in developing countries. These issues include the multiple factors that will influence the acceptance and use of this new HIV prevention

technology at the individual and community levels, and will require strategic planning to promote service delivery, marketing, and programmatic impact. USAID will also support efforts to ensure that future access to microbicides is sustainable by optimizing microbicide manufacturing capacity in developing countries, thereby decreasing the costs of production and distribution.

Looking forward, greater resources will be needed to support ongoing and future clinical trials and to develop and implement the product introduction and HIV prevention programs that will provide microbicides to the people who need them most. Long-term studies on the impact of microbicides on reducing HIV incidence and prevalence in developing countries will also be needed.

The promising product leads, sound strategies, and expanding research capacity currently funded by USAID are generating the progress in microbicide development that will enable and expedite success in this field. USAID has demonstrated that it has the know-how to undertake all of the steps required to develop and introduce safe, effective, acceptable, and affordable microbicides, and that it collaborates effectively and efficiently with other USG agencies, donors, and partners. The results of USAID-supported activities continue to be both impressive and promising and justify a sustained commitment to this effort.

I. The Need for a Microbicide for Women in Developing Countries

Nearly three decades after the discovery of HIV/AIDS, the pandemic continues to spread and threaten the prosperity, stability, and development of nations around the world. An estimated 2.7 million new infections occur every year, infection rates continue to increase in many developing countries, and no cure is available or expected in the near future. Although widespread treatment will help, the greatest impact in mitigating and eventually reversing the pandemic will ultimately be through the development and introduction of new prevention technologies.

An estimated 33 million people worldwide are infected with HIV, and in sub-Saharan Africa, almost 60 percent of those infected are women. The current strategies for preventing HIV infection, including delay of sexual debut, partner reduction, use of condoms, and male circumcision, are not options that can be successfully negotiated by many women in developing countries with concentrated or general HIV epidemics.

Microbicides are an entirely new class of HIV prevention products that, when available, will provide

women with an effective barrier to sexually transmitted HIV and possibly other STIs. The R&D of an effective microbicide, therefore, will help fill the enormous need for a new prevention option for women and will complement other existing or new prevention approaches. For more than a decade, USAID has supported the biomedical and behavioral research needed for the successful development of safe, effective, and acceptable microbicides with low cost and appropriate product characteristics for use in developing countries and through public-sector programs.

II. Microbicides and Health Product Research at USAID

Health research is integral to the ability of USAID to achieve its development objectives worldwide. In partnerships with key public and private sector agencies and non-governmental organizations (NGOs), USAID applies a cycle of assessment, development, pilot testing, and introduction of products, policies, and practices that tackle high-priority disease and health issues in developing countries. This enables USAID to implement effective and sustainable programs that improve health worldwide. Past USAID research investments have led to products that today reach millions, saving lives throughout the developing world – including oral rehydration salts, vitamin A, auto-disable syringes, vaccine vial monitors, and a number of new

family planning methods, among others. In 2005, Congress noted this unique strength of USAID: “With its experience in the developing world, USAID does and should play a valuable role in facilitating international clinical trials, consolidating markets, and finding new opportunities to speed the discovery, development, and delivery of products to improve the lives of those in the developing world.”

As a key implementer of PEPFAR, USAID also plays a critical role in shaping the strategic and technical direction of microbicide R&D to meet developing-country needs. In concert with the Office of the Global AIDS Coordinator (OGAC), USAID will continue the development and eventual introduction of

microbicides to protect against HIV infection and mitigate its spread, especially in regions that are highly affected by this epidemic such as sub-Saharan Africa, India and other parts of Asia, and Latin America.

USAID’s strategy for microbicide R&D is to focus support on moving the most promising and appropriate candidate products available into advanced testing. Clinical trials demonstrating the safety and effectiveness of these products must be completed in order for them to receive approval by the appropriate regulatory agencies. Proof of concept (i.e., demonstrating effectiveness in reducing the risk of HIV acquisition) will speed up the availability of the best product, stimulate the future development of alterna-

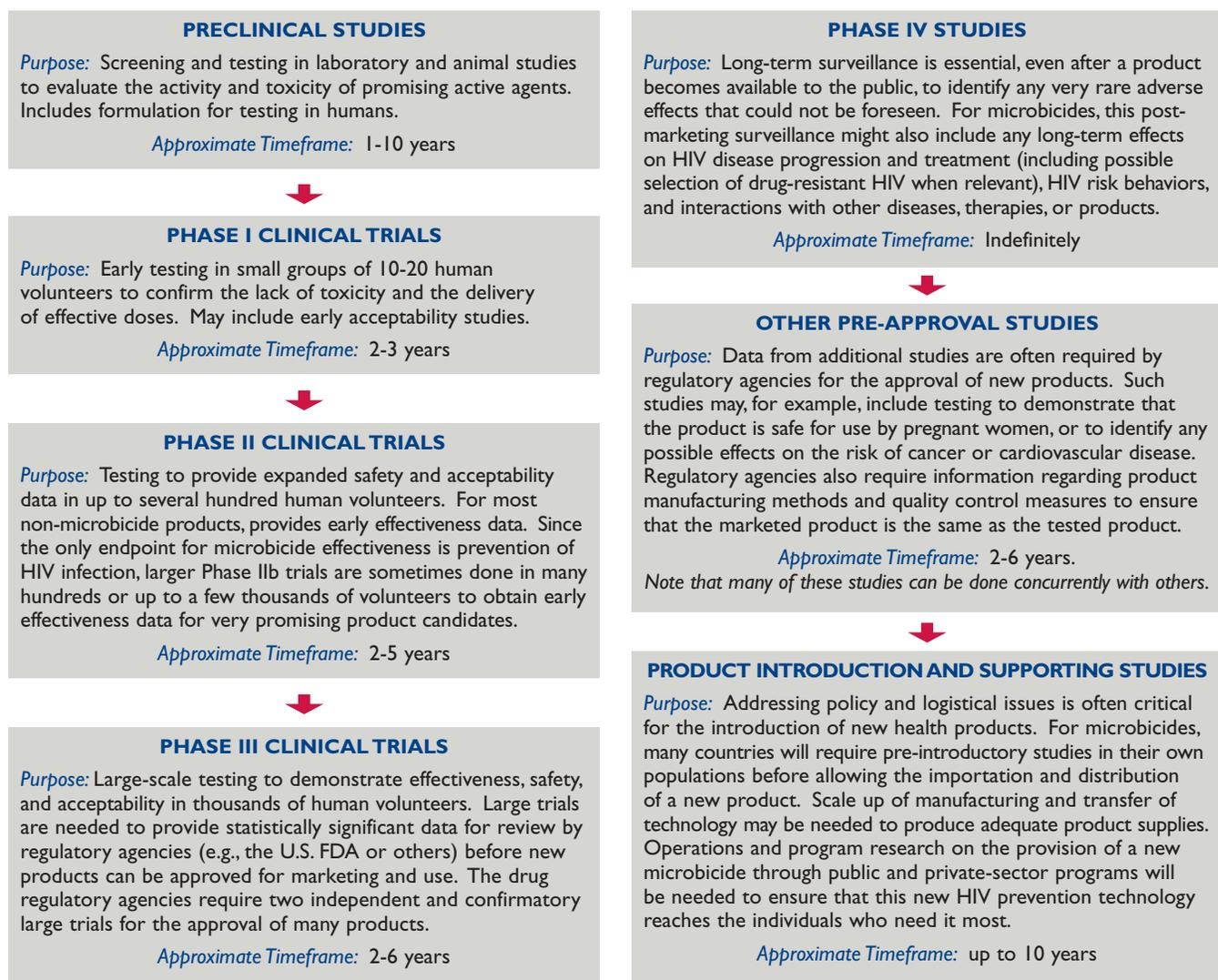
tive or even better products, help identify the most appropriate pre-clinical models for evaluating future candidate products, and attract additional resources, investigators, and donors to this field. The stages involved in the extensive product R&D process are shown for microbicides in the table below.

Financial support for microbicide R&D through USAID increased sig-

nificantly in FY 2001 when Congress allocated \$12 million for this purpose. Determined annually, congressional allocations reached \$45 million in FY 2009. USAID currently implements its microbicide R&D program through cooperative agreements that use subawards as needed to accomplish their research objectives. USAID's extensive field presence and experience in collaboration and research in

developing countries, including in populations with very high rates of HIV incidence (where clinical trials of microbicides must be conducted), are highly instrumental in this effort. USAID is also uniquely positioned to leverage and coordinate the intellectual, proprietary, and financial capital of a host of contributors, including other public-sector agencies, private foundations, and commercial partners.

Stages of Product Research and Development for Microbicides



Note: The timeframes indicated are illustrative and based on typical experience. Some activities in the same or different product development stages can be undertaken simultaneously to expedite progress. As for many other health products, a realistic estimate for the minimum time required for the development of an individual microbicide would be 10-15 years from preclinical testing through product approval by regulatory agencies.

III. The Coordination of the USAID Microbicide Program and Collaborations with Other USG Agencies and Stakeholders

To ensure coordination of federally sponsored microbicide R&D, USAID is in frequent consultation with other USG agencies, including the NIH, CDC, and FDA. This coordination allows the strategic implementation of all preclinical and clinical research, including the prioritization of candidates in the product pipeline. USAID partners with these other USG agencies in developing the U.S. Government Strategic Plan for Microbicide Development (USG Plan), which is currently being updated for 2009 (under the coordination of the NIH Office of AIDS Research). These joint efforts ensure the best use of federal resources and prevent unnecessary duplication of effort.

USAID collaborates in implementing the USG Plan by contributing to the following government-wide objectives:

- *Preclinical development and evaluation of potential microbicide candidates* – to support the discovery, characterization, and early-stage development of potential new active agents for use as microbicides.
- *Formulation and delivery of potential microbicides* – to develop and assess safe, effective, and acceptable formulations and modes of delivery for microbicides, applying knowledge from the

chemical, pharmaceutical, physical, bioengineering, and social sciences.

- *Clinical testing of microbicides* – to assess the human safety, effectiveness, and acceptability of potential microbicides in reducing the transmission of HIV and other STIs and, in the case of products that are also contraceptive, in preventing pregnancy in developing countries and the United States.
- *Behavioral and social science research* – to enhance microbicide development and testing and to better understand factors that will affect future microbicide use and acceptability in developing countries.
- *Provision of training and infrastructure* – to establish, maintain, and strengthen the appropriate training and infrastructure needed to conduct microbicide research internationally and to accelerate future access to microbicides in diverse populations and settings.

The one objective of this USG Plan that USAID's development assistance funding does not support is the conduct of basic biological and physiological research related to microbicides.

The effective coordination of effort among the USG agencies is strengthened not only by extensive consultation, but also by the representation and active contributions of each agency in the technical and programmatic planning and reviews of the other agencies. USAID and a variety of other stakeholders have also collaborated in an effort led by the Alliance for Microbicide Development to complete The Microbicide Development Strategy. This is a very extensive and comprehensive framework for future activities of all stakeholders in the microbicide field, including investigators, donors, and community representatives, and complements the USG Plan. For the microbicide field, this collaborative approach has been both productive and successful in coordinating protocols for preclinical testing, prioritizing promising microbicide candidates, designing clinical trial protocols, building local research capacity, and preparing communities for clinical studies. These collaborations also allow the participating agencies to learn from each other about progress, the state of the art, and best practices, including opportunities to expand standards of care.

IV. The Milestones and Progress to Date of the USAID Program

Preclinical evaluation of potential active agents and the effective formulation of those that merit clinical testing in humans have allowed the USAID microbicide program to make very significant progress. Since 2004, USAID has moved five promising candidates – Savvy™ (C3IG), UsherCell™ (cellulose sulfate), Carraguard™, Tenofovir 1% Vaginal Gel, and oral Truvada™ in women – through the early stages of clinical testing for safety in humans (Phase I and II trials) and into the advanced stages of clinical testing to evaluate the test product's effectiveness in reducing the risk of HIV infection as well as assessing the acceptability of the product to users and providing additional safety data (Phase IIb and III trials).

As in the development of other pharmaceutical products (for which it is customarily necessary to test many leads to find an effective product), the evaluation of two of these candidates, Savvy and UsherCell, was stopped before completion of the respective trials. The Savvy trial was stopped because of concerns about the feasibility of successfully completing the trial since the incidence of HIV at the trial sites was lower than expected. The UsherCell trial was stopped because the number of new infections in the group using the test product exceeded the number of new infections in the control group to a degree that met the pre-defined stopping criteria

for potentially unknown harmful effects of a test product. These reasons for stopping were not expected and only became apparent in the advanced stages of testing when sufficient data were available. Appropriate follow-up investigations are underway to inform future efforts. In both of these cases, the respective Data Safety Monitoring Boards (DSMBs) had conducted an interim analysis of the unblinded trial results (in such a trial, the study personnel do not know if an individual participant receives the test product or the control) while the trial was ongoing and recommended that the trial be stopped. This analysis and the resulting recommendation are in accord with the intended function and authority of the DSMB and ensure that trials are appropriately monitored and meet high scientific and ethical standards.

The Phase III trial with Carraguard, however, is a milestone: It is the first large clinical trial for a microbicide's effectiveness to be successfully completed, although the results (publicly announced in February 2008) indicate that the product, while safe and acceptable, did not significantly prevent infection in this trial. This result may have been due in part to low compliance (or adherence) by some trial participants to the instructions for product use. Efforts to improve compliance in the future are being addressed as part of the behavioral and social science research

described under Objective 4 of the USAID Strategic Plan (see Section VII). Despite the disappointing outcome, the Carraguard trial demonstrates for the microbicide field the feasibility and best practices of conducting large trials with extensive community involvement in developing countries. The findings of this trial are also important because Carraguard may be a key component of some next-generation microbicide formulations. Moreover, it should be noted that important lessons were learned and capacity built as a result of this trial, as well the trials that were stopped before being completed.

In FY 2009, USAID continues to support the international and multi-year Phase IIb and III trials currently underway to evaluate the safety and effectiveness of Tenofovir 1% Vaginal Gel (in the CAPRISA 004 trial) and of Oral Truvada (a combination of Tenofovir and emtricitabine in the FemPrEP trial) in thousands of volunteers (see Objective 3 of the USAID Strategic Plan in Section VII). These trials will be completed in 2010 and 2012, respectively, and will employ specific antiviral agents and unique delivery regimens, which should increase both user compliance and product effectiveness. These large clinical studies are being conducted in collaboration with other agencies and donors to the greatest extent possible to share costs and maximize the speed and efficiency of this work.

V. The Current Priorities of the USAID Microbicide Program

While completion of ongoing clinical trials with the most promising and advanced product candidates is the highest USAID priority, there are simultaneously other strategic research priorities that are critical in addressing technical and other needs in the microbicide field. The research priorities identified in the USAID Microbicide Program are

reviewed and updated at least annually and then shared with USAID partners and the field. These priorities are intended to stimulate, not limit, creative approaches to meet needs and solve problems in microbicide R&D. Investigators requesting USAID funds for microbicide research are expected to take

these priorities into consideration and address them with their USAID funding whenever possible. Subsequent funding and program management decisions can then be made accordingly.

The USAID strategic research priorities for 2009 are shown in the following table.

Priority Area	Description
Novel Delivery Methods	Research is needed on novel delivery methods, including coitally independent methods. These may include a vaginal ring delivery system, sponges, diaphragms, oral formulations, long-acting gels, or other innovative technologies.
Combination Products a. Dual Mechanism b. Dual purpose – microbicide/contraceptive/other	Research is needed for a potential next generation with one or more active agents in a single product that prevent infection through a variety of mechanisms. Microbicides that confer additional reproductive or health benefits are also an objective (e.g., contraceptive microbicides).
Development of New and Existing Leads	In an effort to maintain a full development pipeline, and as the virology and transmission mechanisms of HIV are further understood, research is needed on novel mechanisms for prevention of HIV infection and the application of those technologies to microbicide development. New or existing leads (or products) that can be quickly moved to Phase III trials are of particular interest.
Optimized Clinical Trial Design and Management	Creative solutions are needed for: <ul style="list-style-type: none"> • Accurate and predictive methods of measuring incidence • Improving product compliance/adherence by participants in trials • Prevention of unintended pregnancies in trial participants • Provision and referral for reproductive and/or other health care • Effective preclinical models and biomarkers that accurately predict clinical performance and safety
Clinical Trial Site Coordination	Given the limited number of appropriate clinical trial sites, creative solutions that enable cooperation and coordination are needed to ensure that viable sites are developed and used to their maximum potential and downtime is minimized.
Alternative Trial Designs a. Phase I/II trials with higher predictive value b. Alternative Phase III trial designs	Innovation is needed to validate Phase I & II trial models, as well as preclinical models, with higher predictive abilities in order to determine if a particular product warrants the investment required for a Phase III trial. Additionally, emphasis should be placed on designing clinical trials that provide legitimate, verifiable data that show the safety and effectiveness of microbicide products while reducing the investment of time, human capital, and resources.
Post-Trial Access Issues	Ensuring the broad and equitable distribution of the first generation of emerging microbicide products will require plans for access, uptake, regulatory approval, and supply.

VI. The Review, Selection, and Management of Activities Funded by the USAID Microbicide Program

USAID strives for clarity and transparency about how microbicide activities are reviewed and funded, and it seeks to enhance stakeholder participation in this process.

Microbicide funds are generally provided to implementing partners (known as Cooperating Agencies, or CAs) through cooperative agreements that are usually established for five years and include substantial involvement of USAID technical staff to ensure appropriate use of funds and timely progress. All activities are funded for only one year at a time and require an annual review of their progress, future work plan, and budget to receive additional funding. Following USAID and federal regulations, CAs are usually selected through competitive procurements, but they can also be selected non-competitively when justified by the CA's predominant technical capability, proprietary products, or other unique intellectual property. Extensive opportunities for USAID support are also available to other implementing partners through subagreements with current CAs. In all cases, CAs and their subpartners are selected to provide appropriate technical expertise as part of a sound research plan to meet USAID objectives in microbicide research.

CAs submit annual requests to USAID for support of ongoing and new activities after they have been vetted by their own internal and

external review mechanisms, often including a scientific advisory group. These requests are then evaluated by a review team in the Bureau for Global Health that includes staff with extensive experience in the R&D of microbicides and other health products and expertise, as needed, in HIV prevention and reproductive health programs, public health, virology, clinical trial design and management, social science, regulatory affairs, ethics, community involvement, gender issues, and international development.

USAID reviews the progress of ongoing activities and assesses the technical and programmatic merits of the proposed work plans and budgets of all of the activities submitted. External reviewers are included when additional expertise in a particular area is needed, another informed perspective can help address relevant programmatic and budgetary issues, or clinical trials beyond small Phase I safety trials are under consideration. This annual review often entails an iterative process between USAID and the CAs to ensure that the funded activities reflect both the priorities of USAID and the needs of the broader microbicide field. This allows consideration of all R&D options, including promising alternative leads, across the entire microbicide field.

When advanced clinical trials are proposed, they merit an expanded

level of review that is consistent with the relatively large commitment of resources involved. Such review includes consideration of the participants, clinical sites, investigators, funds, and other resources needed, as well as any potential risks to volunteers and the lost opportunity to support alternative studies. Prior to requesting support for a Phase IIb or III clinical trial to confirm safety and evaluate effectiveness in preventing HIV infection, the CA must have obtained and presented sufficient evidence to justify the advanced clinical trial, including extensive preclinical, pharmacokinetic, animal model, human safety, and other data. Peer-reviewed publication of the available evidence and open discussion of its implications among all experts and stakeholders is preferred, but proprietary product information is also considered whenever necessary to protect intellectual property and future product development interests.

At this stage, independent external reviewers with relevant technical and clinical-trial expertise are engaged to review thoroughly the proposed study rationale and the clinical protocol with objectivity and rigor. Technical, strategic, budgetary, and ethical issues are considered in this review. Efforts are made to ensure the independence of the external reviewers and to minimize any real or perceived conflicts of interest. The Microbicide Working Group being

established in the NIH Office of AIDS Research may be a useful resource for future reviews.

Prior to trial initiation, the proposed clinical protocols are subject to a substantial number of additional reviews, including those by other independent advisory committees, the principal investigators at each clinical site, the institutional or ethical review boards for each engaged institution, and the independent DSMBs when established. The progress of the trial is then regularly evaluated in the following ways: through the tracking of milestones built into the study protocol, by the annual work plan, budget, and management reviews, and by the DSMBs. The progress of the trial is then regularly evaluated by the DSMBs and management reviews and also against the annual work plan, the budget, and milestones built into the study protocol. When possible, these trials are also used to investigate and/or validate more sensitive and predictive preclinical assays for safety and effectiveness, as well as to conduct behavioral or social science studies to understand acceptability and compliance issues and thereby contribute to better clinical testing and better provision and use of microbicides in the future. When these activities occur, they are also reviewed prior to the approval of a study.

For new product research and approval, the FDA is typically involved through the Investigational

New Drug Application (IND), the New Drug Approval (NDA) process, or equivalent procedures of other drug regulatory authorities. These generally include the regulatory review of all preclinical and existing clinical evidence for safety and effectiveness, as well as the study rationale, clinical protocol, and any amendments to the protocol that occur during a trial. Non-U.S. drug regulatory authorities may be involved as well.

USAID also subscribes fully to the USG “Common Rule” for the protection of human subjects in research. All recipients of microbicide funding must comply with these requirements, which ensure review and approval of all research involving human subjects by the appropriate domestic and international institutional and ethical review boards.

Finally, USAID and other stakeholders have an important interest in reviewing any proprietary or intellectual property rights, licenses, sub-licenses, or other relevant agreements that are involved in microbicide R&D supported by the Agency. The effect of these on co-funding, product development timelines, marketing, and public-sector pricing or any other aspect of providing microbicides to the women who need them most is also subject to discussion and negotiation by the appropriate concerned parties, with confidentiality and non-disclosure agreements as necessary.

VII. The Strategic Plan for Continuing Progress with Current Initiatives

The USAID strategic plan for microbicide R&D specifically seeks and funds activities that address the current research priorities (stated in Section V) within each of the USAID Objectives in the USG Plan (in Section III). As noted previously, USAID targets the development of products that will be most suitable for use in developing countries and that are feasible for procurement and provision through public-sector programs.

The activities and funding levels that are described below by objective and level of funding illustrate the implementation of the USAID strategic plan for FY 2008.

Specific activities that address the USAID strategic research priorities within each objective of the USG Plan are described below.

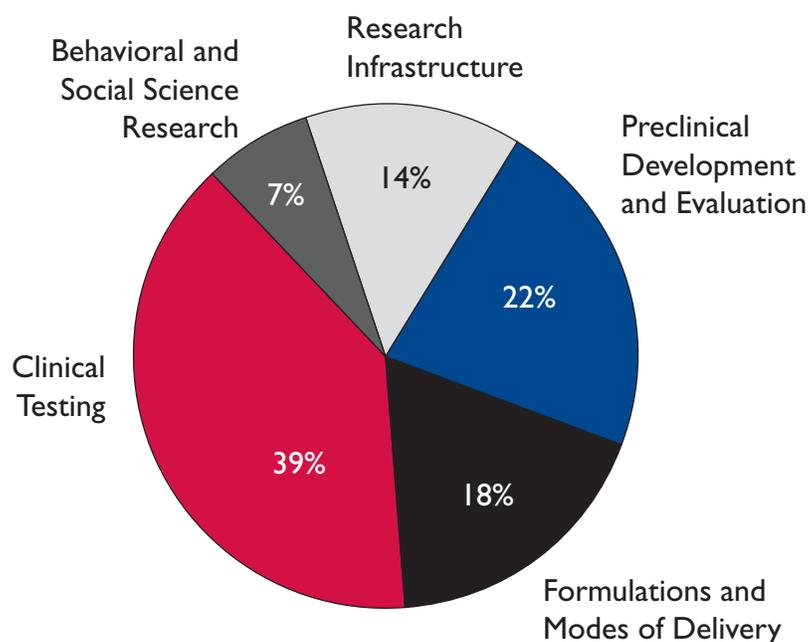
Objective 1: Preclinical development and evaluation of potential microbicide candidates

The USAID strategic plan for microbicide R&D supports the discovery, characterization, and early-stage development of potential new active agents (i.e., active pharmaceutical ingredients or APIs) for use in microbicides, as well as the application and development of improved testing methods.

- As some microbicide candidates using large-molecule non-specific HIV attachment blockers (sulfated polyanions) that moved into advanced clinical trials had disappointing results, more specific

antiviral agents, largely with a single mechanism of action, have been sought as an alternative approach by the field. Current USAID activities include agents that are reverse transcriptase inhibitors (that block HIV replication in cells) or that inhibit

HIV attachment, fusion, and/or entry into human target cells. These activities include ongoing work with Tenofovir, MIV-150, UC 781, Pyrimidinediones, and inhibitors of gp41, NCp7, and CCR5 binding, among others.



USAID Microbicides Research Objectives	FY08 Funding (in thousands)
Preclinical Development and Evaluation	9,757
Formulations and Modes of Delivery	7,847
Clinical Testing	17,731
Behavioral and Social Science Research	2,933
Research Infrastructure	6,368
TOTAL	44,636

- Small animal models are being optimized and applied to characterize the activity and safety of product leads. Transgenic rabbits, for example, are being developed as a more readily available and cost-effective animal model for the study of vaginal infection.
- A variety of biomarkers for safety and effectiveness are being tested and used to assess new leads.

	CAPRISA 004 Study with Tenofovir 1% Vaginal Gel	FemPrEP Study with Oral Truvada for Women
USAID Partner Conducting Trial	Family Health International, CONRAD, CAPRISA	Family Health International
Location (# of Sites)	South Africa (2)	Kenya (2); Tanzania (1); South Africa (2); Malawi (2)
Dates of Initiation and Expected Final Report	May 2007 and December 2010	July 2008 and June 2012
No. of Volunteers to be Enrolled	980 (Enrollment completed in December 2008)	3,900

Objective 2: Formulation and delivery of potential microbicides

The USAID strategic plan supports development of new formulations and modes of delivery for microbicides. These are intended to be not only safe and effective, but also more acceptable to potential users. Greater acceptability may enhance product use in future prevention programs as well as in the clinical trials of these products. Chemical, pharmaceutical, physical, bioengineering, and social sciences are all contributing to these activities.

- As new active agents proceed in development, optimized gel formulations are needed for further characterization in animal models and for future products that would be topically applied.
- Vaginal rings that would release one or more anti-HIV agents, or agents that would simultaneously protect against HIV and other STIs or pregnancy, are being rapidly and collaboratively developed.
- The feasibility of products that prevent HIV, protect the vaginal flora, and are delivered in benefi-

cial and self-sustaining bacterial formulations is advancing.

- Support is essential for the manufacturing of active agents and formulations to be used in pre-clinical studies and clinical trials. Novel production technologies for active agents may also be the key to minimizing microbicide costs and transferring manufacturing technologies to developing countries.
- Existing or novel barrier devices are also being developed and tested as possible microbicide delivery devices. These include diaphragms, female condoms, and vaginal sponges.

Objective 3: Clinical testing of microbicides

The USAID plan continues to place high priority on support for clinical trials of the most promising microbicide candidates to assess their safety, effectiveness, and acceptability in a variety of populations in reducing the transmission of HIV and other STIs, and in preventing pregnancy for products that are also contraceptive.

- USAID will continue to support the advanced Phase IIb and III clinical trials that are currently underway with Tenofovir 1% Vaginal Gel and with oral Truvada™ in women. These multi-year international trials are evaluating the safety, effectiveness, and acceptability of these products in thousands of volunteers and will demonstrate whether these products can meaningfully reduce or prevent the sexual transmission of HIV. Additional information regarding these trials is shown above.
- The data from these trials will allow the FDA and/or European and African regulatory agencies to determine if these products can be approved for marketing and introduction. The initiation and progress of these landmark trials confirm the strength of USAID's collaborations with other agencies and donors to accomplish this work.
- Pharmacokinetic studies are powerful tools to determine if effective levels of active agents are reaching the tissues and cells

that need to be protected from infection as well as how these levels change with time. These studies are instrumental in optimizing microbicide formulations and delivery systems and in defining the regimen needed for effective product use. These studies are currently underway for gel formulations of Tenofovir and UC 781.

- Other clinical studies to evaluate potential biomarkers for safety and effectiveness, distribution and coating properties of gels in women, and tolerance of new formulations in men are also underway.

Objective 4: Behavioral and social science research

As part of the USAID strategic plan, behavioral and social science studies provide unique data on the factors that affect microbicide use and acceptability, especially in developing countries, and thus contribute to the better understanding of these products and their future use in prevention programs. They also provide key information to improve the clinical testing of microbicides and to understand the results of clinical trials.

- Compliance with the recommended regimen for product use is important if new microbicides, regardless of their inherent potency, are to be effective in preventing HIV infection. Acceptability studies and compliance/adherence data from clinical trials are useful for improving product design and

for prioritizing development of design alternatives.

- In clinical trials of microbicides, a meaningful assessment of effectiveness and safety depends on accurate reporting of product use and risk behaviors by the participants. Studies on how and when products are used, and on better methods for collecting sensitive information (including computer-assisted and new communication technologies) are underway.
- Recruitment of appropriate participants is essential for trials to assess safety and effectiveness of new products. New techniques for identifying and reaching communities and individuals where trials can be most effectively conducted and where the benefit of conducting trials will be greatest, are being investigated.
- Informed consent of participants is a cornerstone of conducting clinical research. Achieving and maintaining informed consent in microbicide trials, however, is challenging since trial participation may continue for 12–24 months, the intervals between clinic visits may vary, and some participants may be unduly motivated to participate by the increased access to health care or the locally required level of compensation. Both prospective and retrospective studies comparing different approaches and materials are revealing what works best.

Objective 5: Provision of training and infrastructure

To expedite the development and testing of microbicides at the highest scientific and ethical standards, the USAID strategic plan includes activities to establish, maintain, and strengthen the appropriate training and infrastructure needed to conduct this research internationally. These activities will also accelerate future access to microbicides in diverse populations and settings relevant to USAID programs.

- The USAID program includes site identification activities in selected communities that, based on the presence of clinical resources and high-risk populations, might be appropriate sites for future clinical trials. A systematic and multidisciplinary approach is used to involve local stakeholders in assessing and preparing these potential sites and provides targeted training in research methods, laboratory techniques, ethical review, data analysis, and communications. The intent is to build research capacity (for example, to conduct local HIV incidence studies) that can be successfully sustained in the future to support microbicide and other health research that benefits the community.
- It is increasingly evident that there are many community and national-level stakeholders who are not involved in microbicide development in a technical capacity but have significant roles as community leaders, media specialists, policy makers,

and regulators. USAID supports targeted training and development of information resources in collaboration with the World Health Organization and advocacy groups to enhance community awareness and stakeholder input, and to strengthen clinical studies and future microbicide introduction.

- USAID also supports activities to ensure that after testing is completed, introduction and distribution of microbicides will be expedited in the developing-country populations where the studies were conducted and where the need is greatest. This includes preparing for pre-introduction studies, manufacturing, and procurement, as well as addressing the policy and regulatory requirements for approval and introduction of these products (see Section IX).

The USAID strategic plan for microbicide R&D is currently being implemented through cooperative agreements and/or technical collaboration with a number of partners. These partners include, among others, the following organizations.

- Alliance for Microbicide Development
- CONRAD
- Family Health International
- Global Campaign for Microbicides
- International Partnership for Microbicides
- PATH
- Population Council
- Centers for Disease Control and Prevention
- World Health Organization

These partners and collaborators also have a large number of subawardees that are instrumental in the progress of these activities.

VIII. The Strategic Plan for Advancing the Best Next-Generation Microbicide Leads

As part of the USAID strategic plan for microbicide R&D, advancing the best next-generation leads merits special attention, with consideration of the following goals.

Pursuing new active agents

Consistent with the USAID strategic plan, which gives highest priority to supporting the most promising microbicide leads, a large part of the USAID microbicide budget has supported Phase IIb and III clinical studies in recent years. In contrast to the potential products that previously reached this stage of clinical testing (e.g., Carraguard, cellulose sulfate, Savvy), the two trials that are now ongoing (the CAPRISA 004 study with Tenofovir 1% gel and the FemPrEP study with Truvada) with support from USAID and others use specific antiviral agents (Tenofovir alone or in combination with emtricitabine) and unique delivery regimens (vaginally applied gel before and/or after coitus or an oral tablet) that are intended to increase user acceptability and compliance as well as product effectiveness.

The earlier leads, including Carraguard and cellulose sulfate, were large-molecule, negatively-charged sulfated polysaccharides (polyanions) that blocked HIV attachment. Despite preclinical evidence of strong anti-HIV activity and both preclinical and clinical evidence of safety, in advanced clinical trials, Carraguard was not shown

to be effective in preventing infection, and cellulose sulfate may actually have slightly enhanced infection. Because the reasons for these disappointing results are still uncertain, they are being investigated with USAID support. They may include a lack of significant protective activity in real use, a countervailing negative effect that obscured or exceeded any protective effects, or insufficient adherence to product use by trial participants to allow detection of a protective effect. Although a number of relevant inflammatory and other immunological responses have been examined and not found to be problematic, it remains possible that there are other parameters, such as those related to immune cell function, that are still unknown but significant.

As reflected by the ongoing USAID trials with Tenofovir gel and Truvada, the next-generation focus of USAID and others in the field is now largely on more-specific anti-retroviral (ARV) agents, including Tenofovir, a nucleoside reverse transcriptase inhibitor. Other ARVs under investigation include UC 781 and MIV-150, which are both non-nucleoside reverse transcriptase inhibitors, as well as other agents that prevent viral attachment and/or entry, e.g., by blocking key molecules such as gp41, NCp7, or CCR5 receptors. Initially, the USAID strategic plan was to develop a combination

product with complementary mechanisms of action – for example, one with a specific ARV and a more broadly acting attachment blocker such as a polyanion. Polyanions are now less promising, so other potential combinations are under consideration.

In accord with the USAID research priorities (see Section V) the current USAID strategic plan is to continue formulating and characterizing ARVs that could be combined to yield more effective prevention, and simultaneously be less susceptible to the selection or development of viral resistance. Of most interest are single or combination ARVs that do not select for resistance to any ARVs currently used as therapeutic drugs. Other reproductive health benefits are also desirable (e.g., preventing other STIs or pregnancy), but these attributes may be less achievable with the specific ARVs alone and may require consideration of other classes of agents to be used in combination with ARVs if the latter are shown to be effective.

Each USAID partner involved in the selection of preclinical and clinical candidates has developed an algorithm for rationally evaluating what is known about particular agents and for choosing the most promising candidates. In addition to antiviral activity and inflammatory or other safety parameters, there are many other relevant

parameters to be considered in these choices, including physico-chemical properties that limit the possible options for product formulation, costs that will determine whether a product is viable for USAID and other donor-assisted programs, and access to the intellectual property rights needed to complete product development and ensure access. The selection protocols in use by microbicide development researchers are similar but not identical, and efforts to harmonize the resulting decisions, while fostering legitimate and useful scientific debate, will continue.

Developing new formulations for delivery

The USAID strategic plan also prioritizes the development of alternative delivery systems for next-generation products. Although coitally-dependent gel application may be preferred by some users, options that are not coitally dependent and may or may not be topical gels may be preferred by others. ARVs and other drugs released from vaginal rings and barrier devices are being actively explored. Oral drugs, as used in the FemPrEP trial with Truvada, are also of interest in the context of preventing sexual transmission of HIV. Especially when using ARVs for prevention of infection, it is relevant to know what levels of drug are achieved in key tissues and for what length of time. Agents and formulations that create a persistent barrier that protects between dosing or if a dose is missed could greatly enhance effectiveness. Pharmacokinetic data indicating how the body absorbs

and retains drugs are also instrumental for improving product design, dosing, and delivery, and for defining the instructions for product use.

Reducing product cost

The USAID strategic plan also prioritizes next-generation microbicides that will be inexpensive to manufacture and purchase, and whose manufacturing can be transferred to developing-country settings. This will enable the provision of a cost-effective and accessible microbicide. Collection of data about potential manufacturers and preliminary discussions regarding their interest in microbicide production are underway.

Understanding and avoiding the risk of resistance

The significant challenges entailed in delivering ARV-based products for HIV prevention also need to be clarified and addressed in much greater detail. At present it is not clear how the use of these products, and particular active agents, may increase the risk of selecting resistant virus, especially if infection has already occurred. This risk may require frequent testing of product users for infection status and highly provider-controlled or prescription-only distribution of these products. There are also implications regarding the level of adherence to proper use that will be needed for product safety. These factors may significantly impact the design of products, trials, and provision programs. Strategic combinations of agents that yield the highest barrier to resistance merit more intense investigation.

Considering other non-ARV options

Given the challenges of current ARV-based leads, the possibility of a microbicide that inactivates HIV before attachment, or that blocks attachment through a non-specific effect that is not subject to resistance, for example, remains attractive and would merit investment if sufficiently promising. A product in which resistance was not a concern and that would be suitable for over-the-counter and other wide-scale distribution without HIV testing would be significantly easier to provide and protect more users. PRO 2000 (a naphthalene sulfonate) gel, for which USAID supported some of the preclinical characterization, is now the most advanced candidate in this category. There are now clinical indications that PRO 2000 might be at least partially effective, and the results of further clinical trials with this product are expected in late 2009. Microbicides that simultaneously protect against other STIs, such as herpes simplex virus (HSV) and human papillomavirus (HPV) among others, and/or against pregnancy may also be attractive for many users.

Supporting the next-generation pipeline

Until a microbicide that is proven to be safe, effective, and acceptable is available for regulatory approval and introduction in developing countries, it will be necessary to continue supporting research and development of the most promising next-generation leads. There are promising candidates in the pipeline now, especially given the

possibility of combinations and new delivery options, and a range of alternative leads is needed to ensure robust and cost-effective opportunities for microbicide development in the future.

Continued and strategic targeting of funds is essential to advance these existing and potential leads through clinical testing and the subsequent product development steps if merited. Even when the

first microbicide product is shown to be safe and effective enough to be used in prevention programs, there will still be the need to develop more effective products and broaden the range of options.

IX. The Strategic Plan and Accomplishments to Support Introduction, Distribution, and Use of Microbicides

As the necessary microbicide R&D continues, USAID is simultaneously addressing critical policy and logistical issues to introduce successfully a microbicide product in developing countries once a product has been shown to be safe and effective. The multiple social, cultural, economic, and political factors that will influence acceptance and use of this new HIV prevention technology at the individual and community levels are also being studied. USAID will continue to support behavioral and social science research on the specific factors that could encourage or inhibit acceptance and use in order to guide message development, product promotion, and uptake in the context of behavioral choices made by individuals in relevant communities. Other studies will identify the necessary adjustments in the service delivery environment, assess future marketing potential, and plan for programmatic impact. USAID funding will also be used to optimize manufacturing capacity in developing countries, ensure the lowest possible costs for production, and support technology transfer where possible. The breadth of these USAID initiatives that are preparing for

microbicide introduction, distribution, and implementation are reflected in the activities described below. Many of these initiatives contribute to the success of ongoing preclinical and clinical product R&D activities as well as strategically ensure access to these products once they are available.

Understanding behavior that determines microbicide acceptability and use

A microbicide will not prevent or reduce HIV infection if it is not used. To have an impact on the HIV epidemic, it is essential to develop a microbicide that potential users find acceptable and easy to use. This is also a relevant factor in the successful testing of microbicides in clinical effectiveness trials. If participants are not willing to use the test product, the trial will be a failure regardless of the inherent effectiveness of the product. Behavioral research studies that address the circumstances in which a microbicide would be useful for HIV prevention, and the reasons an individual would or would not use a microbicide in those circumstances, are being conducted by a number of USAID recipients, including

Family Health International, the Population Council, and the World Health Organization. The expertise of USAID and its partners is critical for understanding the key issues and cultural contexts that are involved in these developing-country settings.

Targeting and engaging hidden or hard-to-reach populations will be essential to plan introduction activities effectively when a product is available and to impact the epidemic significantly. This research, including the acceptability of different possible product characteristics (e.g., formulation, mode of delivery, duration of action, effects on other STIs or pregnancy) also informs the product R&D process. Results of this research are already contributing strategically to what a successful microbicide will look like and how it will be introduced in the future.

Involving local communities in clinical research and future introduction

Involving civil society and local communities will be essential for the successful introduction of a microbicide. Even before the start

of clinical trials, significant community consultation and education about test products and procedures are needed to ensure that the potential value of the product being tested, and hopefully introduced in the future, is understood and supported in the community. Local capacity building at trial sites is often needed to conduct product testing, which has broader beneficial impacts on a community and significantly contributes to the preparation for product introduction when possible. Community-level activities with local media and with prevention advocacy groups (e.g., public health workers, women at risk, persons with HIV, or others) also contribute to future introduction. USAID recipients that conduct clinical testing of new microbicides must engage civil society and engender local community involvement as part of their efforts. With USAID support, the Global Campaign for Microbicides works at this level to create and conduct workshops and training and to develop educational materials to ensure that both research and future product introduction are conducted as ethically and equitably as possible.

Modeling the use and impact of microbicides

Realistic and predictive models for the potential impact of microbicides on the HIV epidemic have been developed and refined as part of USAID-supported activities with the Global Campaign for Microbicides in collaboration with the London School of Hygiene and Tropical Medicine. These models evaluate the effectiveness of differ-

ent levels of microbicide use, in different personal circumstances, and with different levels of product effectiveness, as well as in combination with other prevention behavior or with other prevention technologies. Strategically, microbicides may be most effective as part of a “prevention package” of interventions, and modeling is instrumental in understanding what packages may work best in various circumstances. These modeling activities are also very important for planning research and program investments, leveraging support from other donors, and motivating other stakeholders and efforts that will be needed for product introduction.

Developing regulatory policies needed for product approval and distribution

With USAID support, the World Health Organization has conducted four international workshops in India, South Africa, and China that have engaged national and local regulatory officials and other stakeholders from the region in considering how a microbicide for HIV prevention will need to be evaluated, approved, and introduced in their respective countries. These workshops, which focus on the regulatory and policy requirements, organizational capacities, and logistical demands that will need to be addressed, have been very productive to date. The outcomes of these workshops are being organized for publication to ensure the maximum contribution to future product introduction.

Learning lessons from the introduction of other health products

Given the extensive historical experience of USAID in the development and introduction of health products and intervention programs in developing countries, it is critical to apply the lessons learned from these experiences to microbicide introduction. To this end, the Population Council, a key implementer with USAID of past introduction programs for reproductive health products, has already convened a group of experts in the fields of product introduction and social marketing, clinical trials and product development, and reproductive health and HIV/AIDS to identify key features that can guide microbicide introduction efforts. A future effort is being planned to focus specifically on how microbicide introduction could be implemented in the context of “prevention packages” that include other prevention interventions, and how to integrate microbicide introduction with existing HIV prevention and health programs (especially those that are supported through PEPFAR), in order to maximize impact on reducing the epidemic overall. Also planned is the development of a logistical framework to define discretely the steps and timing of activities that need to take place once an effective microbicide is available for introduction. This will include the required activities and timelines for regulatory approval, pre-introduction studies, and mobilization of production and distribution capacity, as well as

appropriate identification and preparation of communities for microbicide introduction and access.

Facilitating communication between stakeholders in microbicide introduction and access

With support from USAID, an annual Microbicides Access Forum has been established by the International Partnership for Microbicides (IPM). This Forum facilitates information exchange and planning for successful introduction and scale-up of microbicides for use by women living in developing countries. IPM develops the meeting agendas in consultation with other USAID-supported partners (including the Population Council, the World Health Organization, and the Global Campaign for Microbicides), as well as other stakeholders in this field. The most recent Forum in Mexico City in August 2008 (1) provided an update on microbicide development and timelines for access planning; (2) presented and discussed recent activities and research related to access, including results from modeling studies; and (3) created an opportunity to share information and facilitate collaboration among participants. Participants identified several important next steps including keeping country-level gatekeepers informed of progress, identifying financing and technical cooperation mechanisms, agreeing on realistic goals for introduction programs, developing tools and guidance for decision-makers to determine criteria for microbicide introduction in different settings, and developing

messaging that is both consistent and appropriate for different country-level stakeholders.

Assessing and developing capacity for future manufacturing and distribution

Developing a microbicide that works will be fruitless if it cannot be manufactured and distributed for introduction and use in the countries where it is most needed. As part of USAID-funded activities conducted by IPM, Regulatory Compliance Initiatives, Inc. assessed the worldwide capability for production of active agents and final microbicide products. The manufacturers of the microbicide candidates and applicators that are now in advanced clinical trials do not have the production capacity needed for introduction of these products in developing countries. Moreover, the current manufacturing facilities for candidates being tested are located in developed countries and not in countries where the products are most needed. Scaling up high-quality manufacturing capacity sufficient for product launch will require timely investment in process development and manufacturing facilities. Manufacturers in some developing countries, such as India, South Africa, and Brazil, could provide attractive options for low-cost, high-volume manufacturing of quality microbicides, and bringing production closer to demand may also reduce shipping and distribution costs, as well as regulatory burdens. To assess this potential capacity, a systematic survey that detailed the technical specifications required for the manufacture of

different types of microbicides was developed and distributed to developing-country manufacturers. The responses were validated with site visits and further assessment of the most promising candidates. Additional information about regulatory oversight and export requirements was collected for the countries in which candidate manufacturers were located. The results of this successful activity are now being widely presented and published, and have not only generated useful discussion, but also have stimulated the development and identification of additional manufacturing candidates as well. USAID has also supported the Population Council to conduct intensive site visits and assessments of manufacturing and marketing candidates specifically for the proprietary microbicide leads of the Population Council.

Focusing on the process and costs of future procurement and distribution

When the first microbicide becomes available, who will pay for it? Since there may not be a large and highly profitable private-sector market for microbicides that can subsidize products provided in public-sector programs, the public and not-for-profit sectors need to be prepared to pay the full cost of buying and distributing this product. USAID has already organized a major international conference session to address this issue with representatives from multilateral donors (the World Bank and the United Nations Population Fund), bilateral donors (the UK Department for International

Development and USAID), and an NGO (the International Planned Parenthood Foundation), with additional discussion by other donors (including the Joint United Nations Programme on HIV/AIDS and the Bill & Melinda Gates Foundation). Each participating organization addressed their decision-making process for adding new products to their portfolio, including their regulatory and registration require-

ments, how their procurement contracts are managed, how the quantities purchased and shipped are determined, how the recipients are chosen, and finally, how the in-country logistics are handled to ensure the intended distribution and availability. The presentations illustrated the different approaches used by donors in selecting the products in their portfolios as well as the critical steps needed to

ensure rapid purchase and distribution in public-sector programs once a microbicide becomes available. Some of the participants reported that the session provoked important internal discussions that have already improved their readiness to respond as soon as microbicides have regulatory approval and are requested for country programs.

X. Looking Forward Programmatically

Once the research, development, and testing of a safe, effective, acceptable, and affordable microbicide are completed, it must be introduced in developing countries as quickly as possible. USAID's experience in pre-introductory studies, distribution and logistics management, capacity building, provider training, service delivery, community involvement, and social marketing, positions the Agency to introduce microbicides and support their appropriate and effective use.

USAID and its partners are uniquely able to undertake these essential multi-stakeholder efforts and will work with the OGAC and other USG agencies to introduce these new products into HIV/AIDS and reproductive health programs and ensure their availability and use to reduce the risk of HIV infection and AIDS in developing countries.

During the next several years, an increased investment in activities to prepare for product introduc-

tion is essential. In addition, the cost of the large, ongoing, multi-site clinical trials will continue or increase, especially in view of the need to ensure that local HIV incidence rates are carefully evaluated before individual sites begin trials. Since it is very likely that additional clinical testing of next-generation product leads will be warranted, further investments will also be necessary to ensure success in the timely development and introduction of these products.

Beyond the next several years, USAID will continue to work with partners to prepare for microbicide manufacturing and introduction in developing countries. Activities will focus on policies, procurement and financing, and logistics and distribution networks within public and private sectors. Countries will need assistance to plan for the relevant information needs of diverse audiences, including policymakers, service providers, community members, and consumers. USAID funding will aid in developing regu-

latory review procedures at global and national levels that will minimize the hurdles to licensing safe and effective microbicides. Research and development of new and improved products may also continue since it is likely that additional and more effective products will be needed before a vaccine for HIV becomes available.

With the regulatory approval of the first effective microbicide, greater resources will be needed for product introduction activities and, eventually, for supporting the HIV prevention programs that will provide these products to the people who need them. The cost of introducing and promoting the use of effective new microbicides in service delivery programs and in other delivery approaches outside the health system will be substantial – and critical to the success of this new prevention option. In addition, it is likely that some regulatory authorities will require post-marketing surveillance studies (Phase IV trials) to monitor side

effects that might only be seen after thousands of women are using these products. Long-term studies on the impact of a microbicide on reducing HIV incidence and prevalence will also be needed.

To succeed in microbicide development, continued substantial funding will be required until a safe and effective microbicide is discovered, tested, and introduced. The promising product leads, sound strategies, and expanding research capacity currently supported by USAID will enable this success.

